Influenza vaccination in young children

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Published in:
Lancet Infectious Diseases

DOI:
10.1016/S1473-3099(11)70221-3

Publication date:
2011

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Santtu Heinonen and colleagues[1] recorded substantial reductions in confirmed symptomatic episodes of influenza in young children who received inactivated influenza vaccine with both a non-randomised cohort and case-control design. The case-control design was applied to quantify any potential selection bias. However, the main discussion in the discipline currently focuses on potential confounding by risk factors because of differential selection for vaccination in non-randomised studies.[2]

Average age, for example, differed greatly between vaccinated and unvaccinated groups, which will bias the effect estimates from the null. The applied stratified analyses for age can effectively control such bias. However, parental smoking behaviour and day care attendance were also different between groups, though not statistically significant, and other potential confounders were not reported or measured.

Therefore, results from an earlier randomised controlled trial among children from the Netherlands might be useful.[3] In that trial, 579 children aged 18–72 months were randomly allocated to receive two doses of parenteral inactivated trivalent sub-unit influenza vaccine and placebo, influenza vaccine and heptavalent pneumococcal conjugate vaccine, or control recombinant hepatitis B vaccine and placebo. During influenza seasons, nose-throat swabs were PCR positive for influenza virus in 4% (12 of 271) of children in the first group and in 5% (11 of 243) of children in the second group. In the control group, the incidence was doubled (9%, 25 of 270) and the efficacy was estimated in both vaccination arms to be around 50% (lower bound 95% CI 3).

These data show that a carefully conducted non-randomised cohort study can produce much the same findings as a randomised controlled trial.[4] Although Heinonen and colleagues' results are in line with our trial data and might support changing vaccination guidelines for young children, cost-effectiveness analysis incorporating seasons with vaccine mismatching and statistical uncertainty in efficacy estimates needs to be done to further convince health politicians and the public.

I declare that I have no conflicts of interest.

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1 Heinonen S, Silvennoinen H, Lehtinen P, Vainionpää R, Ziegler T, Heikkinen T. Effectiveness of inactivated influenza vaccine in children aged 9 months to three years: an observational cohort study. *Lancet Infect Dis* 2011; **11:** 23–29.

2 Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly. *N Engl J Med* 2007; **357:** 1373–81.

3 Jansen AG, Sanders EA, Hoes AW, Van Loon AM, Hak E. Effects of influenza plus pneumococcal conjugate vaccination versus influenza vaccination alone in preventing respiratory tract infections in children: a randomized, double-blind, placebo-controlled trial. *J Pediatr* 2008; **153:** 764–70.

4 Tannen RL, Weiner MG, Xie D. Use of primary care electronic medical record database in drug efficacy research on cardiovascular outcomes: comparison of database and randomised controlled trial findings. *BMJ* 2009; **338:** 1–9.

The results of the investigation by Santtu Heinonen and colleagues[1] into the effectiveness of a trivalent inactivated influenza vaccine in children aged 9 months to 3 years can lead to different conclusions than those drawn by the authors.

The results show that trivalent inactivated influenza vaccine is not effective against influenza B infection, irrespective of age. This finding (which was only reported in the discussion) is attributed to the lineage-level mismatch between the circulating B strain and that included in the vaccine, but could have been expected because several studies have shown that the antibody response induced by trivalent inactivated influenza vaccine against influenza B viruses is poor and often does not provide seroprotection in the first 3 years of life.[2,3] On the basis of this notion, even when the circulating B strain perfectly matches that included in the vaccine, this vaccine is not an ideal means of protecting young children against influenza, especially when substantial B-strain circulation is expected.

Because more immunogenic and effective vaccines than that used by Heinonen and colleagues will probably be approved for children in the near future, we believe that the investigators' recommendation to use trivalent inactivated influenza vaccine in children aged 9 months to 3 years should be less categorical, and that their discussion should have considered data for the new vaccines.

Vesikari and colleagues[3] compared a trivalent inactivated influenza vaccine and an MF59-adjuvanted vaccine, and found that MF59 significantly improved immunogenicity against the B vaccine virus and led to greater than 90% seroprotection rates against matched strains in all children irrespective of age. Moreover, a study of the MF59-adjuvanted vaccine in children aged between 6 months and 6 years[4] showed clinical efficacy rates of 89% against disease caused by vaccine-matched strains and 86% against all circulating strains, which are significantly higher than the 45% and 43% efficacy of trivalent inactivated influenza vaccine reported by Heinonen and colleagues. Live attenuated influenza vaccine has an efficacy of 86% against B strains of the same lineage, 55% against antigenically drifted strains of the same lineage, and 31% against strains of the opposite B lineage that were antigenically unrelated to the vaccine strain.[5]

Finally, Heinonen and colleagues recorded no adverse events. Trivalent inactivated influenza vaccine is well tolerated, but adverse events occurred in all the other studies and this makes us question whether the assessment was made correctly.